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Patentanmeldung Nr. Patent application No. Demande de brevet n°

91403351.9



Den Haag, den
The Hague, 18/11/92
La Haye, le

LLC. Hatten-Heckman

Hatten

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation



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Titre de l'invention:

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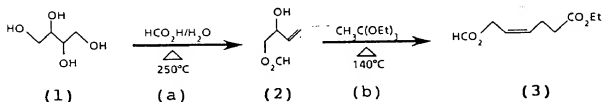
NOVEL PROCESS FOR PREPARING 4-AMINO-5-HEXENOIC ACID

This invention relates to a novel synthesis of 4-amino-5-hexenoic acid using thermal rearrangement reactions, and to the novel intermediates produced thereby.

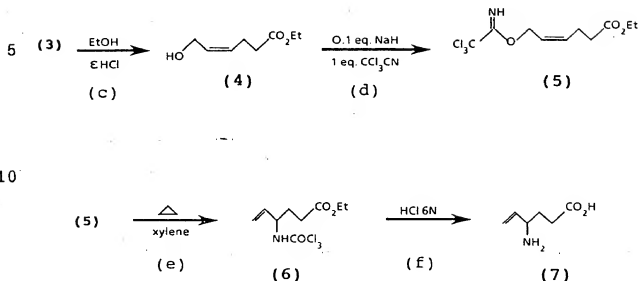
4-Amino-5-hexenoic acid, otherwise known as vigabatrin or vinyl GABA is a GABA-T inhibitor marketed under the tradename SABRIL® for the treatment of epilepsy. (See review article on vigabatrin by S.M. Grant, et al in Drugs, 41 (6): 889-926, 1991).

In essence, this process is based upon known thermal reactions starting from erythritol; said thermal reactions being (1) an elimination process for the formation of a double bond, (2) a Claisen rearrangement and (3) an Overman rearrangement. The involved reaction sequence is depicted by the following reaction scheme.

REACTION SCHEME A



REACTION SCHEME A (cont'd)



wherein Et is ethyl.

Step (a) of the process involves the known thermal rearrangement reaction for the preparation of 4-formyloxy-3-hydroxy-1-butene (2) from erythritol (1) (see Prevost, C., *Ann.Chem.*[10], 10, 398, 1928). Although no work-up is necessary, better yields of a purer compound may be obtained if the product is re-distilled. Step (b) involves a second thermal rearrangement reaction - followed by a hydrolysis - wherein 4-formyl-3-hydroxy-1-butene is heated at 140° - 150°C in the presence of excess quantities of the orthoacetate (4 to 1) under conditions for removal of the *in situ* produced alcohol. (See Johnson W. and Coll, *J.Am.Chem. Soc.* 92, 741, 1970). Following hydrolysis and removal of the excess orthoacetate, the so-produced product ethyl 6-formyloxy-4-hexenoate may be used as is, or it may optionally be subjected to a distillation for purification or it may be subjected to flash chromatography on SiO₂. Alternatively this thermal rearrangement may be effected

using one equivalent of the orthoacetate in an inert solvent which boils around 140° to 150°C (e.g. xylene). The reaction time for these reactions may be monitored by the measurement of the alcohol (methanol or ethanol) which is
5 distilled off.

Step (c) involves the conversion of the formate to its corresponding alcohol by allowing the formate to be stirred at temperatures of about 15° to 25°C whilst in absolute
10 ethanol to which catalytic quantities of alcoholic HCl gas has been added. Step (d) involves the reaction of tri-chloroacetonitrile with ethyl 6-hydroxy-4-hexenoate in the presence of catalytic quantities of NaH (≈ 0.1 equivalent) in an aprotic anhydrous solvent (preferably anhydrous
15 ether) under an inert gas, preferably nitrogen, at about 0°C to form an *in situ* imidate intermediate (5) which, by thermal rearrangement, is converted to ethyl 4-trichloro-acetoamido-5-hexenoate (6); the rearrangement being effected using the techniques of Overman, L.J., *Am. Chem.*
20 *Soc.* 98, 2901, 1976. The final step involves the hydrolysis of the imidate, preferably by acid hydrolysis but alternatively using basic hydrolysis conditions, to produce the desired 4-amino-hexenoic acid, as its HCl salt. The free acid or other pharmaceutically acceptable salts
25 thereof may be obtained by standard procedures well known in the art.

The advantages of this process may be summarized as follows:

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(1) the process does not utilize or form carcinogenic materials, nor are any dangerous reactants or solvents utilized,

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(2) the starting material may be prepared from an inexpensive raw material (potato starch),

- 5 (3) reaction sequence may be done with only one
purification before the final hydrolysis,
(4) a limited number of organic solvents are needed,
(5) the excess of reactants (e.g. trichloroortho-
acetate) and solvents (e.g. xylene) may be
recovered and re-cyclized,
(6) lack of undesirable by-products,
(7) reactions are facile without problems associated
with temperature control and the products may be
10 purified without the need for chromatographic work-
up.

The following example illustrates the novel process of
this invention.

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EXAMPLE 1

4-Amino-5-hexenoic acid

5 STEP A: 4-FORMYLOXY-3-HYDROXY-1-BUTENE: A solution of erythritol (50 g, 0.5 mole) in aqueous formic acid (150 g, 75%) was heated above 100°C, 12 H, then water and formic acid were distilled off and the reaction mixture was heated above 200°C with a Bunsen burner. The product was collected
10 by distillation (b.p. 230°C, 30 g) and should be rectified (b.p. 90°C, 15mn).

¹H NMR (90 MHz) (CDCl₃, TMS) δppm. 3.23 (s, 1 H, OH), 3.6 (m, 1 H, CH), 4.23 (t, 2 H, CH₂), 5.33 (m, 2 H, CH₂=), 5.83 (m, 1 H, -CH=), 8.16 (s, 1 H, HCO₂).

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STEP B: ETHYL 6-FORMYLOXY-4-HEXENOATE: A solution of 4-formyloxy-3-hydroxy-1-butene (1.06 g, 10 mmol) and propionic acid (1 drop) in triethylorthoacetate (6 g, 40 mmol) was heated at 140°C under conditions for
20 distillative removal of ethanol. After 2 H, the excess of ethylorthoacetate was removed by distillation *in vacuo*. The residue was hydrolysed with water and extracted with AcOEt. The product was purified by flash chromatography on SiO₂ (eluant AcOEt: hexane, 2:8) (1 g, 60%) but distillative
25 purification is preferred when larger quantities are involved.

¹H NMR (90 MHz) (CDCl₃, TMS) δppm. 1.26 (t, 3 H, CH₃, J = 6Hz), 2.4 (s, 4 H, (CH₂)₂), 4.1 (q, 2 H, CH₂, J = 6 Hz), 4.6 (d, 2 H, CH₂-C=, J = 6 Hz), 5.73 (m, 2 H, CH=CH), 8.06
30 (s, 1 H, HCO₂).

STEP C: ETHYL 6-HYDROXY-4-HEXENOATE: A solution of 6-formyloxy-6-hexenoate (0.9 g, 5 mmol) in absolute EtOH (10 mL) containing few drops of a saturated solution of
35 alcoholic HCL gas was left 2 H at 20°C. The solvent was

removed *in vacuo* and the residue was used for the next step without further purification (0.7 g, quantitative). This compound was found to be partially decomposed by flash chromatography on SiO_2 .

- 5 ^1H NMR (90 MHz) (CDCl_3 , TMS) δ ppm. 1.26 (t, 3 H, CH_3 , $J = 6$ Hz), 2.4 (s, 4 H, $(\text{CH}_2)_2$), 2.83 (s, 1 H, OH), 4.1 (s, 2 H, $\text{CH}_2\text{-C=}$) 4.16 (q, 2 H, CH_3CH_2 , $J = 6$ Hz), 5.7 (s, 2 H, CH=CH).
- 10 STEP D: ETHYL 4-TRICHLOROACETAMIDO-5-HEXENOATE: Sodium hydride (0.03 g of a 50% dispersion in oil, 0.5 mmol, was added to a solution of ethyl 6-hydroxy-4-hexenoate (0.7 g, 5 mmol) and trichloroacetonitrile (0.6 g, 5 mmol) in anhydrous ether (50 mL) under N_2 at 0°C . After 1 H, ethanol
- 15 (0.5 mmol) was added and the solvent was removed *in vacuo*. The formation of the imidate was controlled by NMR (NH, ~ 8.5 ppm). A solution of the crude imidate in xylene (30 mL) was heated at reflux 48 H. Then the solvent was removed *in vacuo* and the residue was purified by flash chromatography
- 20 on SiO_2 . (eluant AcOEt: hexane, 2:8) to give the title product (1.1 g, $\sim 70\%$).
- ^1H NMR (90 MHz) (CDCl_3 , TMS) δ ppm. 1.23 (t, 3 H, CH_3 , $J = 6$ Hz), 2.0 (t, 2 H, $\text{CH}_2\text{-CH}_2\text{-CO}_2$, $J = 5$ Hz), 2.36 (s, 2 H, CH_2CO_2), 4.1 (q, 2 H, CH_3CH_2 , $J = 6$ Hz), 4.4 (t, 1 H, CH- CH_2 , $J = 5$ Hz), 5.1 (m, 2 H, CH_2), 5.76 (m, 1 H, CH=CH_2), 7.2 (s, 1 H, NH).
- A sample was distilled for analysis (b.p. 150°C , 0.5 mmHg).

Analysis calculated for $\text{C}_{10}\text{H}_{14}\text{NO}_3\text{Cl}_3$:

30	C: 39.69	H: 4.66	N: 4.64
	Found: C: 39.87	H: 4.62	N: 4.49

STEP E: 4-AMINO-5-HEXENOIC ACID: A suspension of ethyl 4-trichloroacetoamido-5-hexenoate (0.3 g, 1 mmol) in 6 N HCl (10 mL) was heated under reflux 6 H. Then the mixture was concentrated *in vacuo*, diluted with water (10 mL), washed
5 twice with Acoet, and dried *in vacuo* to give the title product (0.18 g, 100%). NMR, TLC (NH₄OH:EtOH, 3:7) are identical with those of an authentic sample of 4-amino-5-hexenoic acid.
10 ¹H NMR (90 MHz) (D₂O), δ ppm. (TMS) 1.83 (m, 2 H, CH₂CO₂), 2.33 (m, 2 H, CH₂CH₂) 3.66 (m, 1 H, CH=C=), 5.35 (m, 3 H, CH₂=CH).

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WHAT IS CLAIMED IS:

1. The process for preparing 4-amino-5-hexenoic acid,
and its pharmaceutically acceptable salts thereof
5 which comprises the steps:
 - (a) thermally rearranging erythritol to 4-formyl-3-
hydroxy-1-butene,
 - (b) thermally rearranging 4-formyl-3-hydroxy-1-butene to
ethyl 6-formyloxy-4-hexenoate, followed by the
10 conversion of the formate to its corresponding
alcohol,
 - (c) converting the so-produced ethyl 6-hydroxy-4-
hexenoate to ethyl 6-trichloroacetimidoxo-4-
hexenoate by reaction with trichloroacetonitrile,
15 followed by its thermal rearrangement to its imidate
ethyl-4-trichloroacetoamido-5-hexenoate which, by
hydrolysis is converted to the desired 4-amino-5-
hexenoic acid, and optionally converting said acid
to a pharmaceutically acceptable salt thereof.
- 20 2. Ethyl 6-formyloxy-4-hexenoate.
3. Ethyl 6-hydroxy-4-hexenoate.
- 25 4. Ethyl 6-trichloroacetimidoxo-4-hexenoate
5. 4-Ethyl-4-trichloroacetoamido-5-hexenoate.

ABSTRACT OF THE DISCLOSURE

This invention relates to a novel synthesis of 4-amino-5-hexenoic acid by thermal rearrangements, and to the novel intermediates produced thereby.

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